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ORIGINAL ARTICLE

5α-Reductase inhibitor is less effective in men with small prostate volume and low serum prostatic specific antigen level

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KEYWORDS
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Background/Purpose: Large total prostate volumes (TPVs) or high serum prostate-specific antigen (PSA) levels indicate high-risk clinical progression of benign prostatic hyperplasia. This prospective study investigated the treatment outcome of combined 5α-reductase inhibitor and α-blocker in patients with and without large TPVs or high PSA levels.
Methods: Men aged ≥ 45 years with International Prostate Symptom scores (IPSS) ≥ 8, TPV ≥ 20 mL, and maximum flow rate ≤ 15 mL/s received a combination therapy (dutasteride plus doxaben) for 2 years. Patients with baseline PSA ≥ 4 ng/mL underwent prostatic biopsy for excluding malignancy. The changes in the parameters from baseline to 24 months after combination therapy were compared in those with and without TPV ≥ 40 mL or PSA levels ≥ 1.5 ng/mL.
Results: A total of 285 patients (mean age 72 ± 9 years) completed the study. Combination therapy resulted in significant continuous improvement in IPSS, quality of life index, maximum flow rate, and postvoid residual (all $p < 0.0001$) regardless of baseline TPV or PSA levels. However, only patients with baseline TPV ≥ 40 mL had significant improvements in IPSS-storage subscore, voided volume, reduction in TPV, transitional zone index, and PSA levels. In addition, patients with baseline TPV < 40 mL and PSA < 1.5 ng/mL had neither a reduction in TPV nor a decrease in serum PSA level.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: A high TPV indicates more outlet resistance, whereas elevated serum PSA level reflects glandular proliferation. Thus, patients with TPV<40 mL and low PSA levels has less benefit from 5α-reductase inhibitor therapy. The therapeutic effect of combined treatment may arise mainly from the α-blocker in these patients.

Introduction

Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is a progressive disease.[1–5] With the introduction of selective α-blockers and 5α-reductase inhibitors (5ARI) in the 1990s, the natural history of BPH/LUTS has changed.[3,4] The Medical Therapy of Prostate Symptoms (MTOPS) and Combined Therapy of Avodart and Tamsulosin (CombAT) studies have assessed the long-term outcomes of combination therapy (α-blocker plus 5ARI)[6–8] and suggest that α-blockers cannot reduce the risk of progression without additional treatment with 5ARI. Furthermore, compared with monotherapy, combination therapy significantly improves LUTS symptoms.[6–8]

Compared with the patients in the MTOPS, the CombAT study enrolled BPH/LUTS patients with large total prostate volumes (TPVs, 30 mL vs. 25 mL) and/or higher prostatic specific antigen (PSA) levels (> 1.5 ng/mL). The results indicate that 5ARI may play a role in patients with a risk of disease progression. However, the prostatic size that causes BPH/LUTS might be different between Western and Asian men.[9,10] The effectiveness of combined 5ARI and α-blocker on patients with different prostate size or PSA level remains unknown, especially in the Asian population.

Our aim was to investigate further the therapeutic effect of combination therapy in patients with different prostate size and PSA level. Current European Association of Urology (EAU) guidelines suggest 5ARI should be offered to men who have moderate-to-severe lower urinary tract symptoms and enlarged prostates (> 40 mL) or elevated prostate specific antigen concentrations (> 1.4–1.6 μg/L).[11] We conducted the current prospective multicenter study in the Taiwanese population to compare the treatment outcome of combined 5ARI and α-blocker in patients with and without TPV ≥ 40 mL or PSA ≥ 1.5 ng/mL.

Materials and methods

Study inclusion and exclusion criteria

Male patients aged ≥ 45 years in Taiwan with a clinical diagnosis of BPH were included. The patients also fulfilled the following criteria: moderate-to-severe LUTS with an International Prostate Symptoms score (IPSS) ≥ 8, TPV ≥ 20 mL by transrectal ultrasonography of the prostate (TRUS-P), maximum flow rate (Qmax) ≤ 15 mL/s with minimal voided volume ≥ 125 mL, and serum PSA level < 4 ng/mL. We chose TPV > 20 mL as inclusion criterion based on the regulation by the National Health Insurance in Taiwan. If serum PSA was ≥ 4 ng/mL, TRUS-P-guided biopsy was performed to exclude the presence of prostate cancer prior to initiating 5ARI therapy.

The exclusion criteria were men with: TPV < 20 mL; evidence of prostate cancer; neurogenic bladder due to stroke, spinal cord injury, Parkinson's disease, or other severe neurologic disease; contraindication to performing digital rectal examination or TRUS-P; urinary tract infection or urinary retention within 3 months prior to the study; or receiving any 5ARI, anti-androgen, or phytotherapy treatment 6 months prior to the study.

Study design

This study was a prospective, multicenter, open-label, observational study in men with symptomatic BPH. All eligible patients received dutasteride 0.5 mg once daily with concomitant α-blocker therapy (doxazosin 4 mg per day) for a 2-year period. If patients had postural hypotension after doxazosin treatment, other α-blocker such as tamsulosin (0.2–0.4 mg/day) was used. The self-administered IPSS questionnaire was implemented at baseline, and then repeated every 6 months for 2 years. Uroflowmetry analysis was performed, and voiding volumes, PVR volumes, and serum PSA levels were measured during each visit, whereas TRUS-P was performed to measure prostate volume parameters, including total prostate volume (TPV) and transitional zone index (TZI).

Study endpoint

An expert review of published evidence regarding BPH as a progressive disease defined progression as worsening of symptoms, deterioration of urinary flow rate, increase in TPV, and outcomes such as acute urinary retention (AUR) and the need for surgery either for AUR or symptoms.[12] In the MTOP study, the definition of clinical progression was an increase in IPSS of ≥ 4 points, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection.[6] We added more clear criteria of decreased Qmax and increased PVR in our study. For the preplanned analysis at 2 years, the primary endpoint was the net change in IPSS, uroflowmetric and prostate parameters, and serum PSA level from baseline to 24 months after the first treatment day. The secondary endpoint was comparison of the treatment outcome between patients with and without TPV ≥ 40 mL or PSA ≥ 1.5 ng/mL. The occurrence of clinical BPH progression was defined as IPSS increased by ≥ 4 points, Qmax decreased by ≥ 2 mL/s, and PVR urine volume increased by ≥ 150 mL compared with baseline values, episodes of acute urinary tract infection, episodes of acute urinary retention (AUR), or the need for BPH-related surgery during the treatment period.

Statistical analysis

For all analyses, the variables are presented as the mean ± standard deviation, number, or percentage.

Continuous data in two groups were evaluated by Mann–Whitney U tests to compare the means. Multiple measurement analysis was used to evaluate the significant difference of variables between groups with time points. Categorical data were analyzed using the Chi-square test with Fisher's exact probability test, as appropriate. A p value < 0.05 was considered statistically significant. The statistics program used for the analysis was SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

Patient demographics

A total of 285 patients completed the study up to the 2-year follow-up. The mean age was 72 ± 9 years (range, 45–92 years). There were 150 (52.6%) patients with baseline TPV $\geq$ 40 mL and 135 (47.4%) patients with TPV $<$ 40 mL, whereas there were 158 (55.4%) individuals with baseline PSA levels $\geq$ 1.5 ng/mL and 127 (44.6%) individuals with PSA levels $<$ 1.5 ng/mL.

Changes in IPSS, uroflow, and prostate parameters with time in the overall patient group

From baseline to 24 months, the combination therapy resulted in a significantly continuous improvement in IPSS and quality of life (QoL) index ($p < 0.001$) in the overall patient group. When total IPSS (IPSS-T) was categorized as storage subscore (IPSS-S) and voiding subscore (IPSS-V), all three IPSS groups showed continuous improvement with time ($p < 0.001$). The Qmax and voided volume increased significantly from baseline to 6 months and remained improved up to 24 months. PVR volume showed continuous improvement with time, whereas TPV, TZI, and PSA all showed significant decreases from baseline to 6 months, and steadily improved up to 24 months (all $p < 0.001$).

Changes in IPSS, uroflow, and prostate parameters by baseline TPV ≥ 40 mL or < 40 mL

Combination therapy resulted in significant and continuous improvement in IPSS-T, IPSS-S, IPSS-V, and QoL index in the

Table 1 Changes in IPSS, QoL index, prostate, and uroflow parameters and PVR urine volume from the baseline total prostate volume (TPV) $\geq$ 40 mL (n = 150) or $<$ 40 mL (n = 135).

	Baseline	6 mo	12 mo	18 mo	24 mo	p
IPSS-V						
TPV ≥ 40 mL	8.64 ± 5.64	4.64 ± 4.48	4.35 ± 4.00	3.16 ± 3.59	3.15 ± 3.93	0.316
TPV < 40 mL	7.96 ± 5.10	4.49 ± 4.48	3.19 ± 3.85	3.24 ± 3.83	3.10 ± 3.76	
IPSS-S						
TPV ≥ 40 mL	6.89 ± 3.70	5.08 ± 3.02	4.59 ± 2.64	4.29 ± 2.54	3.75 ± 2.25	0.050
TPV < 40 mL	5.87 ± 3.18	4.39 ± 2.58	4.19 ± 2.53	4.06 ± 2.31	3.66 ± 2.22	
IPSS-T						
TPV ≥ 40 mL	15.5 ± 7.40	9.72 ± 6.24	8.94 ± 5.45	7.45 ± 5.22	6.90 ± 5.33	0.098
TPV < 40 mL	13.8 ± 6.64	8.87 ± 5.67	7.39 ± 5.30	7.30 ± 5.07	6.76 ± 4.89	
QoL index						
TPV ≥ 40 mL	3.68 ± 1.24	2.55 ± 1.00	2.30 ± 0.89	2.19 ± 0.79	2.11 ± 0.80	0.275
TPV < 40 mL	3.41 ± 1.20	2.45 ± 1.03	2.21 ± 0.91	2.19 ± 0.80	2.15 ± 0.77	
Qmax						
TPV ≥ 40 mL	9.92 ± 5.23	11.4 ± 5.45	11.6 ± 5.15	12.9 ± 5.95	12.7 ± 5.51	0.890
TPV < 40 mL	10.7 ± 5.28	11.7 ± 6.00	11.9 ± 5.60	12.2 ± 5.23	12.4 ± 6.15	
Void volume						
TPV ≥ 40 mL	164 ± 93.6	197 ± 111	208 ± 108	227 ± 125	231 ± 138	0.015
TPV < 40 mL	214 ± 128	231 ± 137	226 ± 134	252 ± 139	252 ± 158	
PVR						
TPV ≥ 40 mL	67.8 ± 64.3	64.5 ± 56.7	57.2 ± 53.3	60.4 ± 53.6	57.4 ± 53.1	0.536
TPV < 40 mL	79.9 ± 76.1	61.9 ± 61.3	54.5 ± 56.3	60.6 ± 60.3	65.0 ± 70.6	
TPV						
TPV ≥ 40 mL	60.8 ± 21.4	51.6 ± 20.9	50.1 ± 22.1	48.1 ± 21.5	48.9 ± 21.1	< 0.001
TPV < 40 mL	29.3 ± 6.03	26.0 ± 7.58	26.6 ± 8.20	28.2 ± 22.7	28.0 ± 20.8	
TZI						
TPV ≥ 40 mL	0.52 ± 0.13	0.49 ± 0.13	0.49 ± 0.13	0.48 ± 0.13	0.45 ± 0.12	< 0.001
TPV < 40 mL	0.41 ± 0.14	0.41 ± 0.14	0.38 ± 0.13	0.37 ± 0.13	0.37 ± 0.13	
PSA						
TPV ≥ 40 mL	3.88 ± 4.02	2.71 ± 2.84	2.27 ± 2.20	2.23 ± 2.11	2.29 ± 2.19	< 0.001
TPV < 40 mL	2.06 ± 2.79	1.40 ± 1.59	1.48 ± 1.88	1.50 ± 2.00	1.53 ± 2.02	

IPSS = International Prostatic Symptom score; PSA = prostatic specific antigen; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; S = storage; TZI = transition zone index; V = voiding.

subgroup of patients with baseline TPV $\geq$ 40 mL or $<$ 40 mL (all $p < 0.001$). There was no significant difference in changes in IPSS-T, IPSS-V, and QoL indices between the two subgroups with time, but IPSS-S was significantly improved only in the group of patients with TPV $\geq$ 40 mL (Table 1). Changes in uroflow parameters and PVR urine volume also showed no significant difference between subgroups with TPV $\geq$ 40 mL or $<$ 40 mL, except that voiding volume was significantly increased in patients with TPV $\geq$ 40 mL. Patients with TPV $\geq$ 40 mL showed significantly greater reduction of TPV and PSA values from baseline to 24 months than patients with TPV $<$ 40 mL, whereas TZI showed no difference in reduction.

Changes in IPSS, uroflow, and prostate parameters by baseline PSA ≥ 1.5 ng/mL or < 1.5 ng/mL

From baseline to 24 months, combination treatment resulted in significant and continuous improvement in IPSS-T, IPSS-S, IPSS-V, and QoL index regardless of baseline PSA $\geq$ 1.5 or $<$1.5 ng/mL (all $p < 0.0001$). Uroflow parameters, including Qmax, voided volume, and PVR urine volume, also showed significantly continuous improvement ($p < 0.0001$), but there was no difference between the two subgroups. Prostate parameters, including TPV, TZI, and PSA, all showed significantly greater reduction in the subgroup with baseline PSA $\geq$ 1.5 ng/mL than those with PSA $<$ 1.5 ng/mL (Table 2).

Changes in IPSS, uroflow, and prostate parameters by different baseline TPV and PSA levels

If the patients were divided into subgroups according to baseline TPV $\geq$ 40 or TPV $<$ 40 mL and PSA levels $\geq$ 1.5 or PSA levels $<$ 1.5 ng/mL, there was no significant difference among the four subgroups in all IPSS, QoL index, uroflowmetric parameters, and PVR urine volume from baseline to 24 months after combination treatment. However, TPV showed significantly greater reduction in subgroups with baseline TPV $\geq$ 40 mL regardless of baseline PSA level. PSA also showed significantly greater reduction in subgroups with baseline PSA levels $\geq$ 1.5 ng/mL regardless of baseline TPV. Patients with baseline TPV $<$ 40 mL and PSA levels $<$ 1.5 ng/mL had neither reduction of TPV nor decrease of serum PSA levels (Table 3).

Changes in IPSS, uroflow, and prostate parameters by reduction of TPV by ≥ 20% or < 20% of baseline values

Changes in IPSS, QoL index, uroflow, and prostate parameters in subgroups with TPV reduction of $\geq$ 20% or $<$ 20% from baseline values are shown in Table 4. There was no significant difference between the two groups. Patients without TPV reduction $\geq$ 20% fared as well as those with TPV reduction of $\geq$ 20% after combined dutasteride and α-blocker treatment.

Progression of BPH during the treatment period

During the treatment period, BPH progression was reported in 13 patients with an increase in IPSS by $\geq$ 4 points and in seven with PVR urine volume increase of $\geq$ 150 mL compared with baseline values. Four patients had episodes of AUR. Among those with BPH progression, there were no significant differences in incidence between patients with baseline TPV $\geq$ 40 mL or $<$ 40 mL. In addition, BPH-related surgery was performed only in six patients: all had a baseline TPV $\geq$ 40 mL, but this was not associated with baseline PSA level.

Discussion

PH is a progressive disease.[1–5] As prostate volume or PSA increases, it is evident that the possibility of symptom deterioration and risk of AUR and need for BPH-related surgery increase.[4,13,14] In men with BPH and moderate-to-severe LUTS, the therapeutic benefits of finasteride were observed in the Proscar long-term efficacy and safety study.[15] Finasteride treatment significantly improved IPSS and reduced TPV, with significantly reduced relative risk of AUR and BPH-related surgery in men receiving finasteride versus placebo ($p < 0.001$). The MTOPS study provided valuable information for the combination therapy as the most effective treatment regarding reducing the overall risk of progression and improving LUTS in BPH patients.[6]

Recently, the 4-year CombAT study further demonstrated that the combination of dutasteride and tamsulosin was more effective than either monotherapy in reducing the overall progression in men with BPH and moderate-to-severe LUTS. Furthermore, the CombAT study included patients who were at increased risk of progression by virtue of having larger prostate volume and higher PSA level (TPV $\geq$ 30 mL, PSA $\geq$ 1.5 ng/mL).[7,8]

The MTOPS and CombAT studies have provided valuable information on using risk factors to identify patients whose BPH is likely to progress, and the benefits of using 5ARI to prevent progression in high-risk patients. Thus, the new drug 5ARI could transform BPH from a surgical disease to a medically controllable one. However, current guidelines often lack recommendations on how to choose appropriate treatments for individual needs. Knowledge of the application of modern drug treatments such as combination therapy to appropriate patients is essential because of the financial burden in some countries, such as those with a fixed budget policy for healthcare. Emberton et al[13] proposed a practical BPH treatment allocation by risk stratification. In men with BPH, combination therapy is recommended in patients with moderate-to-severe LUTS in the presence of TPV $>$ 30 mL or PSA levels $>$ 1.4 ng/mL.[8,13,14]

Although TPV $>$ 30 mL was proposed as a cutoff value for selecting patients with LUTS for combined 5ARI and α-blocker therapy, whether men with BPH and TPV $<$ 40 mL also benefit from combination therapy has not been demonstrated. The mechanism of action of 5ARI is supposedly to reduce the prostatic volume; therefore, the TPV and PSA levels should be reduced after 5ARI therapy for more than 1 year. If a patient's TPV and PSA are not reduced after 5ARI therapy, the therapeutic effect of combination therapy might be solely due to the effect of the α-blocker. Adding 5ARI to the α-blocker for treatment of BPH/LUTS is unnecessary.

Table 2 Changes in IPSS, QoL index, prostate and uroflow parameters, and PVR urine volume by baseline PSA level.

	Baseline	6 mo	12 mo	18 mo	24 mo	*p*
IPSS-V						
PSA $\geq$ 1.5	8.35 $\pm$ 5.64	4.38 $\pm$ 4.39	4.08 $\pm$ 4.10	3.01 $\pm$ 3.45	2.72 $\pm$ 3.82	0.376
PSA $<$ 1.5	8.27 $\pm$ 5.09	4.80 $\pm$ 4.58	3.46 $\pm$ 3.78	3.43 $\pm$ 3.99	2.65 $\pm$ 3.82	
IPSS-S						
PSA $\geq$ 1.5	6.37 $\pm$ 3.58	4.65 $\pm$ 2.88	4.49 $\pm$ 2.63	4.20 $\pm$ 2.53	3.61 $\pm$ 2.29	0.890
PSA $<$ 1.5	6.44 $\pm$ 3.40	4.87 $\pm$ 2.80	4.29 $\pm$ 2.55	4.16 $\pm$ 2.31	3.83 $\pm$ 2.16	
IPSS-T						
PSA $\geq$ 1.5	14.7 $\pm$ 7.45	9.03 $\pm$ 6.17	8.57 $\pm$ 5.59	7.21 $\pm$ 5.09	6.32 $\pm$ 5.15	0.473
PSA $<$ 1.5	14.7 $\pm$ 6.64	9.68 $\pm$ 5.74	7.75 $\pm$ 5.20	7.59 $\pm$ 5.21	7.47 $\pm$ 5.03	
QoL index						
PSA $\geq$ 1.5	3.55 $\pm$ 1.27	2.46 $\pm$ 1.03	2.25 $\pm$ 0.91	2.13 $\pm$ 0.78	2.05 $\pm$ 7.08	0.156
PSA $<$ 1.5	3.55 $\pm$ 1.17	2.56 $\pm$ 1.01	2.27 $\pm$ 0.87	2.25 $\pm$ 0.81	2.22 $\pm$ 0.78	
Qmax						
PSA $\geq$ 1.5	10.4 $\pm$ 5.81	11.4 $\pm$ 6.00	11.8 $\pm$ 5.82	12.7 $\pm$ 6.23	13.0 $\pm$ 6.35	0.633
PSA $<$ 1.5	10.2 $\pm$ 4.49	11.7 $\pm$ 5.30	11.6 $\pm$ 4.76	12.4 $\pm$ 4.77	12.0 $\pm$ 5.05	
Void volume						
PSA $\geq$ 1.5	181 $\pm$ 110	201 $\pm$ 113	213 $\pm$ 119	229 $\pm$ 133	238 $\pm$ 146	0.487
PSA $<$ 1.5	196 $\pm$ 119	229 $\pm$ 137	220 $\pm$ 124	251 $\pm$ 131	245 $\pm$ 151	
PVR						
PSA $\geq$ 1.5	77.5 $\pm$ 72.7	67.4 $\pm$ 63.5	59.4 $\pm$ 55.7	63.7 $\pm$ 61.6	63.2 $\pm$ 63.1	0.219
PSA $<$ 1.5	68.7 $\pm$ 67.0	58.1 $\pm$ 52.3	51.5 $\pm$ 53.1	56.5 $\pm$ 50.1	58.3 $\pm$ 60.8	
TPV						
PSA $\geq$ 1.5	54.2 $\pm$ 24.3	46.0 $\pm$ 21.5	45.6 $\pm$ 22.8	44.0 $\pm$ 22.4	44.4 $\pm$ 21.5	0.983
PSA $<$ 1.5	35.5 $\pm$ 14.5	31.2 $\pm$ 15.7	30.8 $\pm$ 13.8	32.2 $\pm$ 24.8	32.3 $\pm$ 23.8	
TZI						
PSA $\geq$ 1.5	0.50 $\pm$ 0.14	0.47 $\pm$ 0.14	0.46 $\pm$ 0.14	0.46 $\pm$ 0.13	0.44 $\pm$ 0.14	0.067
PSA $<$ 1.5	0.42 $\pm$ 0.15	0.42 $\pm$ 0.14	0.41 $\pm$ 0.14	0.40 $\pm$ 0.14	0.38 $\pm$ 0.13	
PSA						
PSA $\geq$ 1.5	4.76 $\pm$ 4.07	3.08 $\pm$ 2.80	2.72 $\pm$ 2.39	2.72 $\pm$ 2.39	2.73 $\pm$ 2.43	0.381
PSA $<$ 1.5	0.85 $\pm$ 0.36	0.85 $\pm$ 0.82	0.87 $\pm$ 0.91	0.84 $\pm$ 0.84	0.94 $\pm$ 1.08	

PSA $\geq$ 1.5 ng/mL: n = 158; PSA $<$ 1.5 ng/mL: n = 127.
IPSS = International Prostatic Symptom score; PSA = prostatic specific antigen; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; S = storage; TPV = total prostatic volume; TZI = transition zone index; V = voiding.

The current *post hoc* analysis of a 2-year prospective, multicenter study in Taiwan provides alternative insights into the effect of dutasteride in symptomatic BPH patients with different prostate size and PSA levels. Like the CombAT study, dutasteride treatment resulted in significant improvements in IPSS, QoL index, and uroflowmetric parameters at 24 months regardless of baseline TPV or PSA level. However, only patients with baseline greater TPV

Table 3 Changes in IPSS, QoL index, prostate, and uroflow parameters, and PVR urine volume from baseline to 24 months among the subgroups with different baseline TPV and PSA levels.

	TPV $\geq$ 40, PSA $\geq$ 1.5 (n = 110)	TPV $>$ 40, PSA $\geq$ 1.5 (n = 48)	TPV $\geq$ 40, PSA $<$ 1.5 (n = 40)	TPV $<$ 40, PSA $<$ 1.5 (n = 87)	*p*
ΔIPSS-V	5.72 $\pm$ 6.23	5.46 $\pm$ 5.38	4.89 $\pm$ 6.16	4.52 $\pm$ 5.02	0.500
ΔIPSS-S	3.03 $\pm$ 3.61	2.17 $\pm$ 3.32	3.45 $\pm$ 3.78	2.23 $\pm$ 3.16	0.134
ΔIPSS-T	8.75 $\pm$ 7.92	7.63 $\pm$ 6.78	8.30 $\pm$ 7.87	6.75 $\pm$ 6.81	0.295
ΔQoL index	1.57 $\pm$ 13.9	1.33 $\pm$ 1.36	1.58 $\pm$ 1.24	1.22 $\pm$ 1.32	0.251
ΔQmax	$-$2.69 $\pm$ 5.88	$-$2.43 $\pm$ 6.94	$-$2.92 $\pm$ 6.31	$-$1.30 $\pm$ 4.52	0.312
ΔVolume	$-$66.2 $\pm$ 134	$-$36.0 $\pm$ 138	$-$70.4 $\pm$ 143	$-$39.2 $\pm$ 139	0.355
ΔPVR	9.43 $\pm$ 84.6	25.6 $\pm$ 100	13.0 $\pm$ 61.2	9.12 $\pm$ 90.5	0.713
ΔTPV	12.2 $\pm$ 17.0	4.33 $\pm$ 8.91	11.0 $\pm$ 10.9	$-$0.36 $\pm$ 24.4	$<$ 0.001
ΔTZI	0.07 $\pm$ 0.16	0.05 $\pm$ 0.18	0.07 $\pm$ 0.10	0.03 $\pm$ 0.16	0.393
ΔPSA	2.20 $\pm$ 3.22	1.63 $\pm$ 2.03	$-$0.11 $\pm$ 1.50	$-$0.07 $\pm$ 0.82	$<$ 0.001

IPSS = International Prostatic Symptom score; PSA = prostatic specific antigen; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; S = storage; TPV = total prostatic volume; TZI = transition zone index; V = voiding.

Table 4 Changes in IPSS, QoL index, prostate, and uroflow parameters and PVR from baseline to 24 months among subgroups with TPV reduction $\geq$ 20% or $<$ 20% of baseline values.

	TPV reduction $\geq$ 20% (n = 130)	TPV reduction $<$ 20% (n = 155)	p
ΔIPSS-V	5.15 ± 5.74	5.22 ± 5.74	0.915
ΔIPSS-S	2.74 ± 3.51	2.66 ± 3.45	0.858
ΔIPSS-T	7.88 ± 7.54	7.88 ± 7.33	0.999
ΔQoL index	1.32 ± 1.41	1.52 ± 1.28	0.210
ΔQmax (mL/s)	−2.46 ± 5.62	−2.09 ± 5.90	0.592
ΔVolume (mL)	−50.7 ± 147	−55.8 ± 129	0.757
ΔPVR (mL)	19.6 ± 87.6	6.67 ± 84.9	0.209
ΔTPV (mL)	17.2 ± 11.3	−1.80 ± 19.4	$<$ 0.001
ΔTZI	0.04 ± 0.15	0.06 ± 0.16	0.232
ΔPSA (ng/mL)	1.37 ± 2.85	0.85 ± 2.18	0.085

IPSS = International Prostatic Symptom score; PSA = prostatic specific antigen; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; S = storage; TPV = total prostatic volume; TZI = transition zone index; V = voiding.

($\geq$ 40 mL) or higher PSA ($\geq$ 1.5 ng/mL) had any significant reduction in TPV or PSA level. Patients with TPV $<$ 40 mL but PSA $\geq$ 1.5 ng/mL had a mild reduction in TPV, but patients with TPV $<$ 40 mL and PSA $<$ 1.5 ng/mL did not reduce TPV or PSA at all.

A large TPV usually indicates more outlet resistance, while elevated serum PSA level could be a reflection of glandular proliferation. Eckhardt et al[16] found a positive correlation between prostate volume and Schäfer's obstruction grade. The degree of bladder outlet obstruction defined by the increment in the Abrams-Griffiths number was also significantly correlated with TPV as measured by TRUS-P.[17] This result indicates that the effect of 5ARI (dutasteride) on prostatic hyperplasia is clearly demonstrated in patients with larger TPV and higher PSA. Because the TPV did not change after combination therapy, the therapeutic effect of combination therapy on those with small BPH and PSA levels $<$ 1.5 ng/mL is likely to be due to the α-blocker, and 5ARI does not appear to contribute to the improvement of IPSS or uroflow parameters.

This study also shows that improvements in IPSS, QoL index, and uroflow parameters are not associated with TPV reduction following combined 5ARI and α-blocker treatment. Patients with a TPV reduction $<$ 20% have the same treatment outcome as those with reduction $\geq$ 20% of baseline TPV. Although TPV and PSA reduction seems greater in patients with greater BPH, patients without TPV reduction also have similar improvements in IPSS and uroflow parameters. The therapeutic effect of α-blockers might be greater in patients with small BPH and little reduction in TPV. However, patients with a large TPV at baseline are more likely to progress and BPH-related surgery is needed during long-term combination therapy. Therefore, the true therapeutic effect of 5ARI involves the reduction of prostate volume and application of a safety valve for long-term medical treatment on large BPH.

A high PSA level may be due to large TPV, chronic inflammation, or occult prostate cancer. Recently, chronic inflammation in the prostate has been considered to play an important role in the development of LUTS in patients with BPH.[18,19] Patients with high serum C-reactive protein (CRP) levels and BPH are associated with higher storage LUTS, implying a possible link between chronic inflammation and sensory nerves in the lower urinary tract.[20,21] The present study shows that combined dutasteride and α-blocker treatment effectively results in significant improvement in IPSS storage subscores and voiding volume in patients with TPV $\geq$ 40 mL compared with TPV $<$ 40 mL. This finding implies that the therapeutic effect of 5ARI may lie beyond reduction in prostatic volume or bladder outlet obstruction. Reduction in TPV is associated with a reduction in PSA: not only is prostatic hyperplasia inhibited, but chronic inflammation can also be reduced after 2 years of 5ARI therapy. Last, data from a subgroup analysis of MTOPS suggested that the presence of prostatic inflammation may indicate a greater likelihood of treatment efficacy with a combination of α-blockers and 5ARI therapy.[22] Although our results did not show a greater effect on IPSS and uroflow parameters for patients with TPV $\geq$ 40 mL compared with those with TPV $<$ 40 mL, reductions and PSA and a better improvement in storage IPSS subscore and voiding volume were noted only in the TPV $\geq$ 40 mL group, suggesting that 5ARI therapy is suitable only for patients with a larger BPH.

There are some inherent limitations in this study. First, we could not perform experiments using a placebo arm as controls because of ethical reasons. Second, we performed only baseline prostate biopsy for patients with high PSA levels but did not perform protocol biopsy of the prostate, except when the possibility of prostate cancer arose. However, the study findings may reflect the real world practice in Asian men with clinical BPH.

In conclusion, a high TPV indicates more outlet resistance, whereas elevated serum PSA level reflects glandular proliferation. Thus, patients with TPV $<$ 40 mL and low PSA levels have less benefit from 5ARI therapy. The therapeutic effect of combined treatment may arise mainly from the α-blocker in these patients.

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